changes in intrathoracic pressure. Leftward shift of the ventricular septum during inspiration though may impair filling of the LV and, consequently, diminish Vp.

Finally, we would like to solicit the authors' comments, and we wonder whether a respiratory variation in Vp may be a marker for hemodynamic compromise due to pericardial effusion.

Mario Togni, MD
Division of Cardiology
University of California
San Diego School of Medicine
UCSD Medical Center
200 W. Arbor Street, No. 8411
San Diego, California 92103
E-mail: mtogni@ucsd.edu

Ralph Shabetai, MD, FACC
Daniel Blanchard, MD, FACC

PII S0735-1097(00)01070-6

REFERENCES

1. Garcia MJ, Smedira NG, Greenberg NL, et al. Color M-mode Doppler flow propagation velocity is a preload insensitive index of left ventricular relaxation: animal and human validation. J Am Coll Cardiol 2000;35:201–8.
2. Nishikawa Y, Roberts JP, Talcott MR, Dysko RC, Tan P, Klopfenstein HS. Accelerated myocardial relaxation in conscious dogs during acute cardiac tamponade. Am J Phys 1994;266(5 Pt 2):H1935–43.

REPLY

The recent implementation of new Doppler echocardiographic methods for the assessment of diastolic function has improved our understanding of this complex entity. Standard indices of transmitral flow are hampered by their dependency on loading conditions and left ventricular (LV) relaxation and have therefore been unable to differentiate a patient with normal (normal relaxation and preload) versus pseudonormal (impaired relaxation and increased preload) LV filling (1). More recently, the velocity of flow propagation into the LV (Vp) has been shown to provide an estimate of LV relaxation (2,3). Takatsuji et al. (4) studied a large group of patients with normal relaxation, delayed relaxation and pseudonormal pulsed Doppler patterns of LV filling confirmed by hemodynamic findings. While pulsed Doppler indices showed the typical "U-shaped" distribution from normal to delayed relaxation in pseudonormal patients, color M-mode Doppler Vp was equally low between the last two groups. Furthermore, their study also showed a strong negative correlation between τ and Vp, despite a wide variability in LV filling pressures among the three groups of patients, suggesting that Vp was less influenced by preload. In a study published in the January 2000 issue of the *Journal* (5), we demonstrated in controlled experimental settings that Vp was not affected by preload reductions in dogs undergoing caval occlusion and humans during partial bypass.

The letter of Togni et al., describing the changes in color M-mode flow propagation velocity (Vp observed in a patient with cardiac tamponade, is of significant interest. The authors demonstrate 1) significant respiratory variability of Vp during cardiac tamponade, increasing during inspiration and 2) a significant decrease in Vp after pericardiocentesis. A possible explanation for the respiratory variability observed may be periodic misalignment between the direction of flow and the M-mode cursor, changing the Doppler angle of incidence. This is likely to occur in the presence of a large pericardial effusion, when increased inspiratory venous return to the right heart can result in lateral translation of the LV. We agree with the authors, who conclude that the overall higher Vp during tamponade is likely due to a catecholamine-driven increase in LV relaxation. The fact that Vp decreased after pericardiocentesis, when venous return to the LV should increase, further supports that Vp is a preload-insensitive index.

Mario J. Garcia, MD, FACC
The Cleveland Clinic Foundation
Section of Cardiovascular Imaging
Department of Cardiology/F15
Cleveland, Ohio 44195
E-mail: garciam@cesmtp.ccf.org

PII S0735-1097(00)01069-X

REFERENCES

1. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865–75.
2. Brun P, Tribouilloy C, Duval AM, et al. Left ventricular flow propagation during early filling is related to wall relaxation: a color M-mode Doppler analysis. J Am Coll Cardiol 1992;20:420–32.
3. Stugaard M, Risoe C, Ihlen H, Smiseth OA. Intracavitary filling pattern in the failing left ventricle assessed by color M-mode Doppler echocardiography. J Am Coll Cardiol 1994;24:663–70.
4. Takatsuji H, Mikami T, Urasawa K, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J Am Coll Cardiol 1996;27:365–71.
5. Garcia MJ, Smedira NG, Greenberg NL, et al. Color M-mode Doppler flow propagation is a preload insensitive index of left ventricular relaxation: animal and human validation. J Am Coll Cardiol 2000;35:201–8.

Apolipoprotein E Genotype and Coronary Heart Disease

We have read with interest the article by Frikke-Schmidt et al. (1), which concludes that male carriers of the Apo E epsilon43 and epsilon44 genotypes are particularly susceptible to ischemic heart disease.

We studied 220 men younger than 50 years of age (mean age 43 ± 5 years; range 26 to 50 years) and diagnosed with coronary artery disease (CAD). The polymorphisms of the apolipoprotein E (Apo E) were determined and compared to a control group of 200 healthy individuals matched with patients for age and ethnicity and residents in the same region (Asturias, northern Spain). We analyzed the principal cardiovascular risk factors, and during hospitalization and after fasting for 12 h a lipid profile study was carried out.

The Apo E genotype frequencies are summarized in Table 1. In our population, the Apo E gene and genotype frequencies were similar between patients and controls. Also, Apo E gene and genotype frequencies did not differ between patients with or without diabetes, or with or without hypertension. In addition, average biochemical values did not differ between the genotypes of each of the four polymorphisms.

Compared to other Caucasian populations, we found a lower frequency of the Apo Eϵ4 allele. These data are in agreement with

JACC Vol. 37, No. 1, 2001
January 2001:328–38

Table 1. Apo E Genotype Frequencies in Patients and Controls

Apo E	Patients (n = 220)	Controls (n = 200)	p
ϵ33	174 (79%)	151 (75%)	NS
ϵ34	32 (15%)	28 (15%)	NS
ϵ44	4 (2%)	2 (1%)	NS
ϵ23	9 (4%)	18 (9%)	NS
ϵ24	1	1	NS

previous reports that showed the lowest frequency for the ϵ4 allele in Southern European populations (2–6). The low frequency of the ϵ4-frequency allele among Mediterraneans has been linked with a decreased risk of CAD in these populations, compared to Northern Europeans, who have the highest ϵ4-frequency and the highest rate for CAD in Europe.

In accord with this, we did not find a significant difference for the Apo E gene and genotype frequencies between patients and controls, suggesting that the ϵ4 allele is not a strong risk factor for early CAD in our population. The role of Apo E genotypes in the risk of CAD has been analyzed previously (7,8).

For the ϵ4-allele, a significantly increased frequency in patients compared to healthy controls has been described in some but not all studies. These discrepancies could be partly attributed to the fact that these studies analyzed different populations worldwide, and the ϵ4-allele could be a risk factor in association with other genetic or environmental factors.

Alberto Batalla, MD
Department of Cardiology
Cabueñes Hospital, Gijon
Spain

Ruth Alvarez, PhD
Sergio Hevia, MD
Julián R. Reguero, MD
Eliecer Coto, PhD
Department of Cardiology
Laboratory of Molecular Genetics
Central Hospital of Asturias
Oviedo
Spain

PII S0735-1097(00)01072-X

REFERENCES

1. Frikke-Schmidt R, Tybjaerg-Hansen A, Steffensen R, Jensen G, Nordestgaard BG. Apolipoprotein E genotype: epsilon32 women are protected while epsilon43 and epsilon44 men are susceptible to ischemic heart disease. J Am Coll Cardiol 2000;35:1192–9.
2. James RW, Boemi M, Giansanti R, Fumelli P, Pometta D. Underexpression of the apolipoprotein E4 isoform in an Italian population. Arterioscler Thromb 1993;13:1456–9.
3. Valveny N, Esteban E, Kandil M, Moral P. Apo E polymorphism in Spanish and Moroccan populations. Clin Genet 1997;51:354–6.
4. Muros M, Rodriguez-Ferrer C. Apolipoprotein E polymorphism influence on lipds, apolipoproteins and Lp(a) in a Spanish population underexpressing apo E4. Atherosclerosis 1996;121:13–21.
5. Tiret L, de Knijff P, Menzel H, Ehnholm C, Nicaud V, Havekes LM. Apo E polymorphism and predisposition to coronary heart disease in youths of different European populations: the EARS study. Arterioscler Thromb 1994;14:1617–24.
6. Van Bockxmeer FM, Mamotte CDS. Apolipoprotein epsilon homozygosity in young men with coronary heart disease. Lancet 1992;340:879–80.
7. Wilson PWF, Myers RH, Larson MG, Ordovas JM, Wolf PA, Schaefer EJ. Apolipoprotein E alleles, dyslipemia and coronary heart disease: the Framingham Offspring Study. JAMA 1994;272:1666–71.
8. Ilveskoski E, Perola M, Lehtimäki T, et al. Age-dependent association of apolipoprotein E genotype with coronary and aortic atherosclerosis in middle-aged men. Circulation 1999;100:608–13.

REPLY

We appreciate the comments of Batalla et al. concerning our paper on premature coronary artery disease (CAD). The authors share with us their data on young adults admitted with acute coronary syndrome. They also provide follow-up information in the subgroup with normal cholesterol compared to those with abnormal cholesterol levels as defined by the ratio of total cholesterol to high density lipoprotein levels. There are some similarities between their data and ours; however, major differences exist. Similar features include the fact that both studies evaluated young adults age 50 years or younger. Second, both populations were high risk, with high rates of categorical risk factors. For instance, the rate of smoking was 73% in their study compared to 75% in our group. The rate of hypertension was 36% and diabetes mellitus was 9% in Batalla et al., which is similar to the 39% and 12% in our study for those two conditions, respectively.

Hypercholesterolemia was 77% in their report. The rate of hypercholesterolemia was 46% in our report, but the two studies used different definitions. A comparison between the two studies is limited by major differences in methodology and incomplete data provided by the authors. First, their report involves exclusively male subjects, whereas as many as 30% of our population were young women. Second, their analysis was done by comparing two groups based on cholesterol levels. We, in contrast, compared two groups based on irrefutable evidence of significant CAD. Furthermore, they do not specify the time period over which the data was collected. For this reason we do not know the frequency of admissions for premature CAD. Next, what percent does this represent for admissions of acute coronary syndrome?

We commend the authors for providing follow-up information on outcomes. In their report, after 32 months' follow-up there were no differences in outcome between those with abnormal compared to normal cholesterol. They conclude that the absence of differences in outcomes represents a lack of benefit of low cholesterol in young adults with high rates of smoking. This interpretation is similar to an earlier report by Jee et al. (1) in subjects without previous CAD. The suggestion that low cholesterol does not confer a benefit for secondary prevention in young adults has important clinical implications. There are, however, other possible explanations. This was an observational study that did not consider the effect of treatment. It is possible that the lack of outcome differences may be attributable to some treatment benefit in the group with high cholesterol who were treated according to current guidelines. This actually proves the merit of guidelines for secondary prevention.

Finally, a secondary explanation concerns the small sample size. With a small sample size in each group it is possible that one would need a much longer duration of follow-up to appreciate differences. We do agree that, in young adults with multiple cardiovascular risk factors, the best strategy to reduce recurrent events in the short term should be based on managing all